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ARTICLE

Altered prefrontal connectivity after acute heroin administration during cognitive control

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Abstract

Neuroimaging studies have reported reduced activity in a broad network of brain regions during response inhibition in heroin-dependent patients. However, how heroin in an acute dose modulates the neural correlates of response inhibition and the underlying brain connectivity has not yet been investigated. In this double-blind placebo-controlled study, we used functional magnetic resonance imaging to examine whether acute heroin administration changed whole brain activity during response inhibition in 26 heroin-dependent patients. We then applied dynamic causal modelling to investigate the effect of an acute dose of heroin on the functional interactions between the dorsal anterior cingulate cortex (dACC) and the bilateral inferior frontal gyri (IFG). Heroin acutely reduced dACC activity, as well as the inhibition-induced modulation of connectivity from the dACC to the right IFG compared with placebo. Furthermore, dACC activity was positively related to false alarm rates after placebo but not heroin administration. These results suggest that acute heroin administration impairs cognitive control in dependent patients by reducing the activity in the dACC activity and the functional connectivity from the dACC to the right IFG.

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Key words: Acute heroin administration, anterior cingulate cortex, effective fronto-cingulate connectivity, inferior frontal gyrus, response inhibition.

Introduction

Drug addiction is recognized as a severe relapsing brain disorder characterized by an overwhelming compulsion to seek and use drugs (Leshner, 1997). Impairments in inhibitory control, including a compromised ability to exert control over drug urges or to inhibit impulsive drug-driven behaviour have often been reported in drug addiction (Perry and Carroll, 2008; Chambers et al., 2009). For instance, it has been shown that heroin and cocaine dependents have a significantly lower degree of impulse control than normal controls (Lee and Pau, 2002; Fernández-Serrano et al., 2012).

Functional magnetic resonance imaging (fMRI) studies have shown that disrupted response inhibition functioning in drug addiction is associated with abnormal prefrontal cortex (PFC) activity including the dorsal anterior cingulate cortex (dACC) and inferior frontal gyrus (IFG) (Goldstein and Volkow, 2011). In heroin-dependent subjects, significant deactivations during response inhibition as indexed by the Go/No-Go task were observed in the bilateral medial PFC, left middle frontal gyrus (MFG), insular and parahippocampal gyrus, as well as in the ACC and IFG (Lee et al., 2005; Fu et al., 2008), suggesting that dysfunctional activity in these regions may be responsible for the weakened inhibitory control in heroin addiction. Some subdivisions of the ACC are anatomically connected with the PFC (Barbas and Pandya, 1989; Morecraft et al., 1993) likely reflecting a functional interplay. Indeed, ACC activation is frequently linked with activation of the IFG (Koski and Paus, 2000). More recently, increased connectivity has been shown between the ACC and right IFG during inhibition processes (Cieslik et al., 2013). In heroin-dependent subjects, abnormal functional connectivity of the dACC with bilateral IFG has been reported during resting state (Wang et al., 2013). Previous theories proposed that such dysfunctional PFC–ACC connectivity renders them susceptible to compulsive drug seeking (Li and Sinha, 2008).

The present study comprised two parts investigating the acute effects of heroin on the neural correlates of response inhibition. In a first step, we completed our previous analysis which was focused on the acute effect

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of heroin on the right IFG activity during its dual role in response inhibition and stimulus-driven attention allocation (Schmidt et al., 2013c). Compared with the previous study, here we included not only successful trials but also error trials in order to achieve robust ACC activation, given that the ACC is primarily activated in error monitoring during the Go/No-Go task in healthy subjects (Rubia et al., 2003). The ACC is of particular interest as acute heroin administration reduces ACC perfusion in dependent patients (Denier et al., 2013). Furthermore, because previous studies demonstrated an association between ACC activity and performance during response inhibition in drug addiction (Leland et al., 2008; Goldstein et al., 2010), we also tested whether such a relation existed after the administration of heroin and placebo.

In the second part, we used a model-based effective connectivity approach (dynamic causal modelling (DCM); (Friston et al., 2003) to explore whether heroin acutely affected the inhibition-induced modulation of connection strengths between the dACC and IFG. DCM allowed us to evaluate the directionality of the causal interactions between the dACC and IFG and the modulatory effect of contextual experimental conditions. We particularly used DCM to examine how heroin acutely affected the modulation of connectivity from the dACC to the IFG induced by the No-Go trials. DCM has been successfully used to study effective connectivity in different brain disorders (Seghier et al., 2010) including drug addiction (Ma et al., 2014) and recent studies demonstrated its sensitivity to detect pharmacological manipulations from fMRI data (Grefkes et al., 2010; Schmidt et al., 2013b). Although response inhibition also involves brain regions outside the PFC (Simmonds et al., 2008), we restricted our connectivity analysis on ACC-IFG interactions based on previous evidences showing (1) functional ACC-IFG connectivity associated with response inhibition (Kemmotsu et al., 2005; Cieslik et al., 2013), (2) dysfunctional activity in the ACC and IFG during response inhibition in drug addiction (Goldstein and Volkow, 2011) including heroin addiction (Forman et al., 2004; Lee et al., 2005; Fu et al., 2008) and (3) reduced perfusion in the ACC and PFC after acute heroin administration in patients (Denier et al., 2013). On the basis of these studies, we hypothesized that acute heroine administration would reduce dACC and IFG activation as well as their inter-regional connectivity.

Method

Patients

A total of 26 heroin-maintained outpatients (mean age: 41.1 ± 6.8 yr; 19 male) with opioid dependence according to ICD-10 criteria were recruited from the Centre of Substance Use Disorders of the Psychiatric University Hospital of Basel. The included patients were older than 18 yr and had a past history of intravenous heroin consumption with a current heroin-assisted treatment for at least 6 months with an unchanged heroin dose during the previous 3 months. Subjects reported their years of education (mean: 10.23 ± 2.54 yr), smoking behaviour (cigarettes per day: mean: 21.46 ± 9.19), age of first heroin use (mean: 18.88 ± 3.46 yr), years of dependence (mean: 20.54 ± 6.56 yr), and daily heroin dose (mean: 326 ± 130.97 mg). The Barratt Impulsiveness Scale was used to assess trait measure of impulsivity (mean: 67.16 ± 7.2) (Patton et al., 1995). Patients with additional physical disease or psychiatric disorder including comorbid conditions like other substance dependencies were excluded from participation. Clinically experienced psychiatrists conducted a structured clinical interview for DSM-IV Axis II Disorders (SCID-II) to assess the diagnosis of comorbid personality disorders. Patients were told to abstain from drug consumption other than the prescribed heroin administration for the duration of the study. Nevertheless, 8 patients were tested positive for cannabis and 12 patients for cocaine at one or both points of the measurement. The study was approved by the local ethics committee and registered with http://clinicaltrials.gov (ID NCT01174927). After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion.

Experimental design

As previously reported (Schmidt et al., 2013a, c), placebo (saline solution) and heroin were administered through an indwelling intravenous catheter over a period of 30 s, using a cross-over, double-blind, vehicle-controlled design. Heroin hydrochloride was dissolved on site in 5 ml of sterile water and aspirated into a syringe as previously described (Stohler et al., 1999). Subjects who received their individualized dose of heroin before the first scanning session received 5 ml of placebo before the second session, and vice versa. Furthermore, on both sessions all subjects received both heroin and placebo. That is, the subjects who received heroin before scanning were administered vehicle after scanning (i.e. 60 min after the first injection), whereas the subjects who received placebo before scanning were administered heroin after scanning.

fMRI paradigm: Go/No-Go task

The event-related paradigm was conducted 30 min after drug administration. The task is a well-validated paradigm requiring either the execution or the inhibition of a motor response (Rubia et al., 2006; Borgwardt et al., 2008). The basic Go task is a choice reaction time paradigm in which arrows appear pointing either to the left or right side lasting for 500 ms with a mean ISI of 1800 ms (jitter range of 1600–2000 ms). On 'Go trials', subjects are instructed to press a response button as quickly as possible according to the direction of the arrow. In 11% of the trials, so-called 'No-Go' trials, arrows pointing

upwards appear and participants are required to inhibit their motor response. On another 11% of the trials, arrows pointing left or right at a 23° angle are presented and subjects are told to respond to these the same as for Go stimuli (even though they pointed obliquely). In total, there were 24 No-Go, 160 Go and 24 oddball trials with a task-duration of approximately 6 min.

fMRI image acquisition and data analysis

Scanning was performed on a 3T scanner (Siemens Magnetom Verio, Siemens Healthcare, Germany) using an echo planar sequence with 2.5 s repetition time, 28 ms echo time, a matrix size of 76×76 and 38 slices with 0.5 mm inter-slice gap, providing a resolution of $3\times3\times3\ mm^3$ and a field of view of $228\times228\ mm^2$. In total, 160 volumes were acquired.

Data analysis was performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). All volumes were realigned to the first volume, normalized into a standard stereotactic space (MNI: Montreal Neurological Institute), and smoothed using a 8 mm full-width-at half-maximum Gaussian kernel. During model specification, onset times for all Go and No-Go trials were convolved with a canonical haemodynamic response function, in contrast to our previous study where only successful trials were considered (Schmidt et al., 2013c). Serial correlations were removed using a first-order autoregressive model and a high-pass filter (128 s) was applied to remove low-frequency noise. Six movement parameters were also entered as nuisance covariates. Instead of slice timing, temporal derivative were included in the informed basis set, which can account for ±1 s of changes in timing. Subject-specific condition effects for the main effect of task (No-Go>Go contrast) were computed using t-contrasts, producing a contrast image propagated to the second-level analysis. Whole-brain differences between both treatment conditions were evaluated by second-level paired *t* test analysis. The statistical threshold was adjusted to provide a family-wise error (FWE) of $p<0.05$ (based on the spatial extent of clusters of voxels thresholded at $p<0.001$; cluster-forming threshold (Petersson et al., 1999)), corrected for multiple comparisons.

Statistical analysis

Differences on task performances as indicated by the probability of inhibition and the sensitivity index d′ were previously analysed and published elsewhere (Schmidt et al., 2013c). Beyond these previous analyses, here we evaluated task performances with respect to false alarm rates. Pearson's correlation analysis was conducted to assess the relation between ACC activity and false alarm rates. ACC activity for the 'No-Go>Go' contrast was obtained from the first eigenvariate of a sphere with 6 mm radius around the peak of activation. Finally, a multivariate GLM analysis was used to explore whether the acute heroin effect on whole brain activity, task performance and effective connectivity (dependent variable) was confounded by the impact of cannabis and cocaine consumption (fixed factors).

Effective connectivity analysis: dynamic causal modelling (DCM)

We used DCM10 (revision No. 4290) as implemented in SPM8 to analyse effective connectivity. In DCM for fMRI, the dynamics of the neural states underlying regional BOLD response are modelled by a bilinear differential equation that describes how the neural states change as a function of endogenous interregional connections, modulatory effects on these connections, and driving inputs (Friston et al., 2003; Stephan et al., 2007). The endogenous connections represent coupling strengths in the absence of inputs to the system (independent of the task), whereas the modulatory effects represent context-specific and additive changes in coupling (e.g. task-induced alterations in connectivity). The modelled neuronal dynamic is then related to the measured BOLD signal using a hemodynamic forward model (Stephan et al., 2007). Here, we particularly examined how heroin acutely affected the modulation of connectivity from the dACC to the IFG induced by the No-Go trials (modulatory effect, matrix B in DCM).

Time series extraction from region of interest

Regional time series from the dACC and bilateral IFG for each subject were extracted from spherical volumes of interest with 6 mm in diameter as previously done (Brázdil et al., 2007; Schlösser et al., 2010) that were centred on the treatment-specific maxima of the No-Go>Go contrast within the anatomical mask using the first eigenvariate of voxels above a subject-specific *F*-threshold of $p<0.01$. The anatomical mask composed of the dACC and bilateral IFG was taken from the Automated Talairach atlas (Aal) in WFU Pick Atlas toolbox (Tzourio-Mazoyer et al., 2002). Treatment-specific activation in the bilateral IFG and dACC are depicted in Fig. 1*a*, while the maxima are reported in the Supplementary Table S1. One patient revealed no activated voxels under these criteria and was therefore excluded from the connectivity analysis.

Model design

We assumed the same network layout of endogenous connections between the dACC and bilateral IFG, where all three regions were reciprocally connected. We first constructed two families varying in whether the visual (driving) input (Go trials) was entered only into the dACC (F1) or into all three regions of interest (F2). Furthermore, within each family, different models were constructed depending on where the modulatory effect of the No-Go trials was exerted. Specifically, we contrasted models where the No-Go trials were allowed to modulate (i) no connection between the dACC and

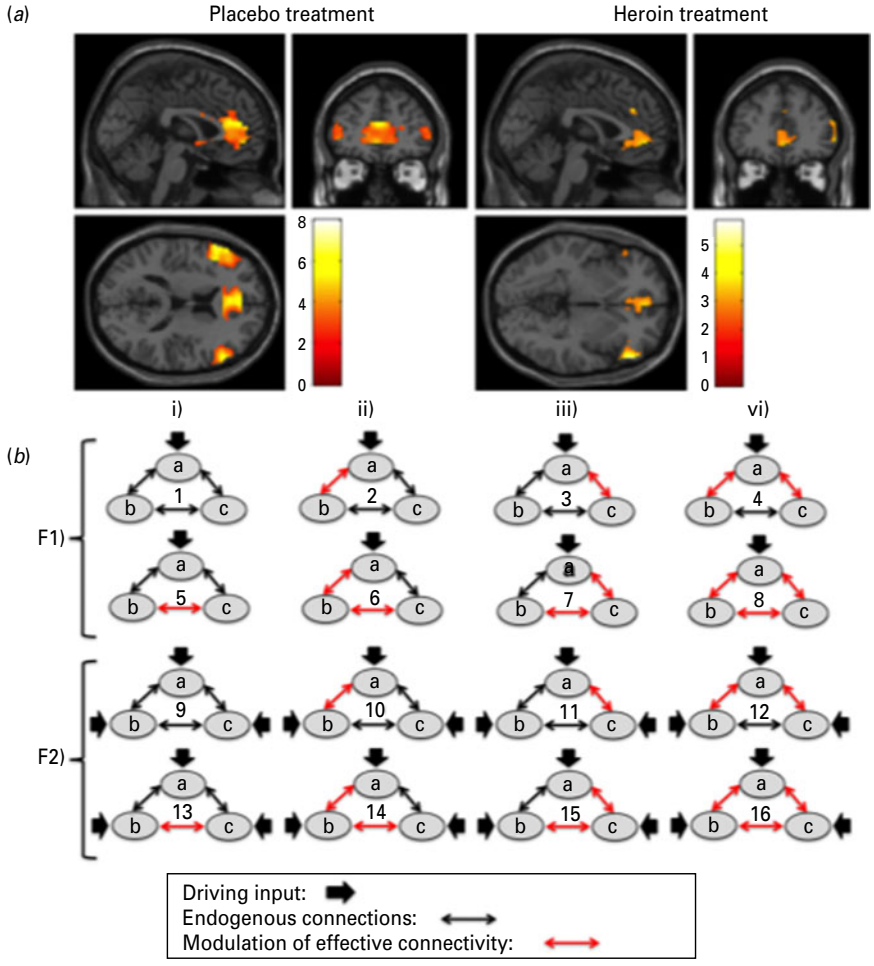

Fig. 1. (*a*) Significant activation in the dACC and bilateral IFG during response inhibition after placebo (FWE corrected for multiple comparisons at cluster-level at $p<0.05$) and heroin administration (uncorrected for multiple comparisons at cluster-level at $p<0.05$). (*b*) Dynamic causal models characterizing different options for modulation of connectivity between the dACC (*a*) and left (*b*) and right IFG (*c*) induced by No-Go trials, which were compared among each other to determine the most likely. dACC dorsal anterior cingulate cortex; FWE family-wise error, IFG inferior frontal gyri.

bilateral IFG (first column in Fig. 1*b*), (ii) connections from the dACC to the left IFG (second column in Fig. 1*b*), (iii) connections from the dACC to the right IFG (third column in Fig. 1*b*), or (iv) connections between the dACC and bilateral IFG (fourth column in Fig. 1*b*). Furthermore, within both subfamilies F1 and F2, additional modulation of inter-hemispheric connections between the left and right IFG was added in half of the models. In total, 16 models per patient were compared. For a graphical overview of the model design see Fig. 1*b*.

Bayesian model selection and averaging

In a first step, Bayesian model selection (BMS) was used to determine the most likely model (family of models) among all other models considered (Penny et al., 2010). BMS rests on comparing the evidence of a predefined set of models (see model architecture). The model evidence is the probability of observing the empirical data, given a model, and represents a principled measure of model quality, derived from probability theory (Penny et al., 2004). A random-effects BMS approach was applied, which is capable of quantifying heterogeneous data while being extremely robust to potential outliers (Stephan et al., 2009). One common way to summarize the results of random effects BMS is to report the exceedance probability (EP) of each model, i.e. the probability that this model is more likely than any other of the models tested, given the group data (Stephan et al., 2009). BMS was applied over both treatment conditions separately, as it is possible that response inhibition may be differently generated after acute heroin administration.

Given that different models may be found to be optimal across both conditions, Bayesian model averaging (BMA) has been recommended as standard approach for clinical DCM studies (Stephan et al., 2010). BMA averages posterior parameter estimates over models, weighted by the posterior model probabilities. Thus, models with a low posterior probability contribute little to the estimation of the marginal posterior.

Table 1. Whole brain activity No-Go>Go contrast over all patients irrespective of treatment (n=52)

Brain region	Cluster size	MNI (x, y, z)	Z score
Right inferior frontal gyrus	169	(56, 32, 2)	6.19
Left inferior frontal gyrus	30	(−56, 22, 20)	5.26
Right superior parietal lobule	102	(24, −46, 68)	5.44
Right superior frontal gyrus	164	(2, 54, 32)	5.43
Right middle frontal gyrus	96	(34, 24, 44)	5.14
Left middle frontal gyrus	19	(−24, 62, 12)	4.92
Left anterior cingulate cortex	29	(0, 48, −4)	5.04
Precuneus/posterior cingulate cortex	23	(2, −48, 38)	4.78

Activations are reported at p<0.05 family-wise error (FWE)-corrected for multiple comparisons across the whole brain. MNI Montreal Neurological Institute.

Statistics of DCM parameters

After BMA, we used the resulting posterior means from the averaged DCM to examine differences between treatments. In this article, we focus on WM-induced changes in connectivity. Thus, we test for treatment differences in the modulatory parameters only using paired t-test.

Results

Task performance

We found no significant differences concerning false alarm rates between the placebo (mean±S.D.=6.68±8.50) and heroin treatment (mean±S.D.=7.01±10.46) (T=−0.113; p=0.911).

fMRI results

Inhibition-related whole brain activity

Response inhibition (No-Go>Go contrast) was associated with bilateral activation in the IFG, MFG, right superior parietal lobule (SPL), right superior frontal gyrus (SFG), left ACC and precuneus/posterior cingulate cortex (Table 1).

Whole-brain effect of acute heroin administration

Relative to placebo, significantly decreased dACC activity after acute heroin administration was found (FWE-corrected for multiple comparisons across the whole brain at peak and cluster-level at p<0.05) (Fig. 2*a*). Furthermore, we found a significant positive correlation between dACC activity and false alarm rates under placebo (r=0.621; p=0.001) but not heroin (r=0.167; p=0.435) (Fig. 2*b*).

DCM results

Bayesian model selection

In a first step, we determined which of the regions was the most likely input region. Dynamic causal models with driving inputs into the dACC (F1) were significantly superior to alternative models (F2) in which the IFG was also assumed to receive external inputs; this was found in the placebo (EP(F1)=97%, EP(F2)=3%) and heroin condition (EP(F1)=98%, EP(F2)=2%) (Fig. 3*a*). The comparison of single models revealed that model 4 which included modulation of connectivity from the dACC to the left and right IFG induced by the No-Go trials as the best fitting model in the placebo (EP=15.61%) and heroin condition (EP=15.4%) (Fig. 3*b*).

Acute heroin effect on effective connectivity

To examine the acute heroin effect on effective connectivity, we compared the parameter estimates from subject-specific DCMs that were averaged using BMA separately for the placebo and heroin condition, resulting in six connectivity parameters, which could be compared. We found that the modulation of connectivity from the dACC to the right IFG induced by the No-Go trials was significantly reduced by heroin (mean±S.D.=0.0007±0.0039) compared with the placebo treatment (mean±S.D.=0.0052±0.0057) (T=3.66, p=0.001, Bonferroni-corrected for multiple comparisons) (Fig. 4 and Supplementary Table S2).

Notably, no significant relations were found between dACC activity, false alarm rates, ACC->right IFG connectivity and the consumption of cannabis and cocaine consumption (Supplementary Table S3).

Discussion

The main findings of this fMRI study are that an acute dose of heroin reduced the activation in a key region of response inhibition in heroin-maintained patients, namely in the dACC, as well as the inhibition-induced modulation of connectivity from the dACC to the right IFG. Furthermore, dACC activity was related to false alarm rates after the placebo but not heroin administration.

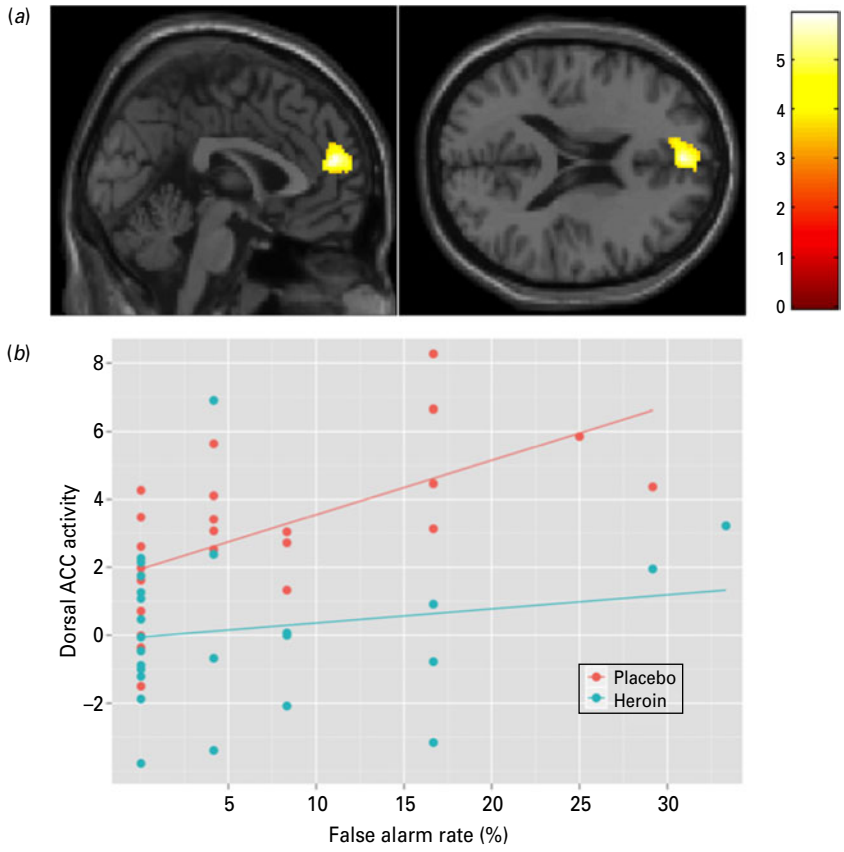

Fig. 2. (*a*) Significant heroin-induced reduction of dACC activity (MNI coordinates of peak focus x=0, y=52, z=18 with a cluster-size of 370 voxels) during response inhibition relative to placebo (FWE-corrected for multiple comparisons at peak and cluster-level at $p<0.05$). (*b*) Significant positive correlation between dACC activity and false alarm rate after placebo ($r=0.621$; $p=0.001$) but not heroin administration ($r=0.167$; $p=0.435$). dACC dorsal anterior cingulate cortex, MNI Montreal Neurological Institute, FWE family-wise error.

Heroin effect on ACC activity

Consistent with a recent meta-analysis (Criaud and Boulinguez, 2013), we found significant inhibition-related activation in the IFG, MFG, right SPL, right SFG, and ACC. We further observed that the dACC activity was significantly reduced after acute heroin administration compared with placebo in heroin-dependent patients. The reduction of ACC activity can probably be explained by the acute heroin-induced reduction in ACC perfusion in the same patients (Denier et al., 2013), although such a relation and its specific direction needs to be explicitly explored in further studies. Attenuated ACC activity during cognitive control has previously been reported in newly admitted and abstinent heroin-dependent subjects. The authors concluded that this disrupted frontal inhibitory function may contribute to the impulsive behaviour in people who abuse heroin (Lee et al., 2005) and that this impairment still continues in protracted abstinent withdrawal state, might render them vulnerable to later relapses (Fu et al., 2008). Furthermore, decreased ACC resting state connectivity has been observed in abstinent heroin-dependent individuals compared with healthy non-drug subjects, while the degree of which correlated negatively with the ACC response to heroin-related cues (Liu et al., 2011). As irregularity of the ACC may lead the impaired inhibitory control in heroin-dependent subjects (Fu et al., 2008), the negative correlation of the ACC between rest and the task may reveal the role of the inhibitory network for heroin-related cue processing (Liu et al., 2011). Our result extends these findings in active and abstinent addicts by showing that a single dose of heroin acutely reduced the dACC during response inhibition in heroin-dependent patients. In contrast to the present findings, we recently observed no significant ACC activation during the Go/No-Go task after placebo and heroin administration if only successful inhibitions were considered (Schmidt et al., 2013c). Given that the ACC is primarily activated in error monitoring during the Go/No-Go task (Rubia et al., 2003), the ACC activation found in the present study is likely driven by error responses, as not only correct but also incorrect trials were incorporated into the analysis. Under this perspective, Forman and colleagues showed that opiate addicts exhibited an attenuated ACC activity in response to errors compared with a healthy control group (Forman et al., 2004), similar as observed in cocaine addiction (Kaufman et al., 2003). This failure of error-related ACC

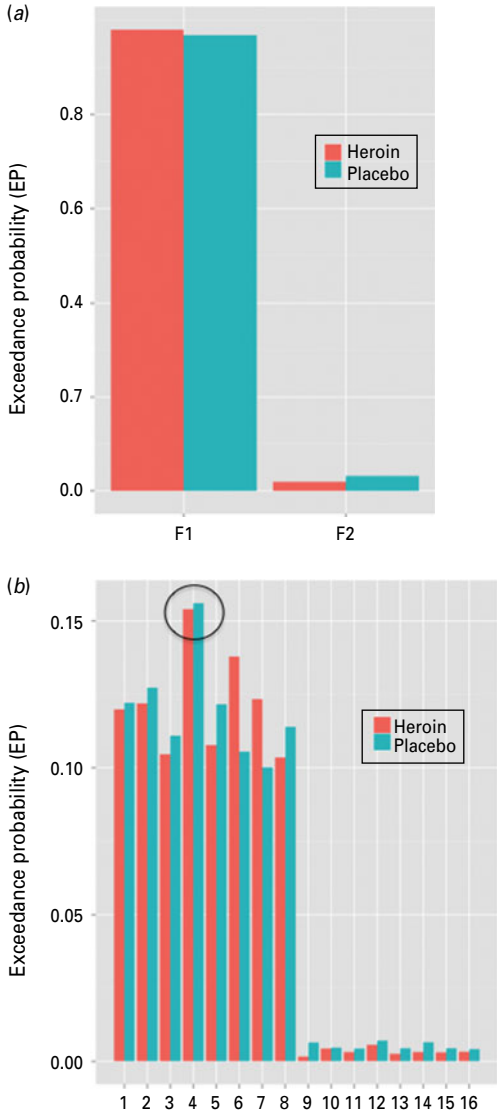

Fig. 3. Bayesian model selection on family (*a*) and single model level (*b*) for both treatment conditions separately. BMS results are reported in terms of exceedance probabilities. BMS Bayesian model selection.

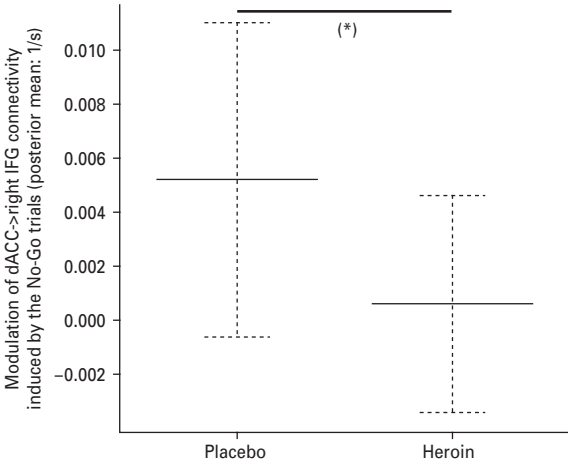

Fig. 4. Modulation of connectivity from the dorsal ACC to the right IFG induced by No-Go trials after heroin and placebo administration. The y-axis denotes the mean for all study participants and all 16 dynamic causal models (using Bayesian model averaging) with regard to the posterior mean of the modulatory effect; this encodes changes in connection strength induced by the No-Go trials. Note: Significant between treatment-differences at $p=0.001$ (Bonferroni-correction for multiple comparisons). ACC anterior cingulate cortex, IFG inferior frontal gyri, dACC dorsal anterior cingulate cortex.

activity in opiate-dependent subjects has previously been replicated (Yücel et al., 2007). These findings suggest that abnormal dACC activity may partly underpin key addiction-related phenomena, such as poor inhibitory control of drug-related behaviour in the face of adverse consequences. Although we cannot infer on differences to healthy controls, our results suggest that heroin acutely reduces dACC activity in response to false alarms compared with the placebo treatment in dependent patients. This interpretation is supported by the positive correlation between ACC activity and false alarm rates after placebo but not heroin administration. That is, patients under placebo showed a linearly increase in ACC activity as a function of false alarm rates, which was not present after acute heroin administration. Importantly, Forman et al., investigated subjects actively enrolled in methadone maintenance treatment; at the time of scanning, five participants had not yet received any methadone, while eight participants already received the methadone. Thus, it is difficult to disentangle whether the decrease in error-related ACC activity was evident already before the methadone treatment (would reflect the placebo condition in the present study) or only in those patients who have already received their daily dose (the heroin condition in our study). Thus future research is needed to study how the error-related ACC activity differs between healthy subjects, short and long-term abstinent dependents and patients undergoing maintaining treatments (methadone *vs.* heroin).

Heroin effect on fronto-cingulate effective connectivity

In the second part, we used DCM to examine how heroin acutely affected the modulation of connectivity from the dACC to the IFG induced by the No-Go trials. In line with a previous DCM study of infrequent target detection (Brázdil et al., 2007), Bayesian model selection revealed that models in which the ACC served as input regions better fitted the data than models in which the IFG was assumed to receive external inputs. Comparison of single models revealed that the model with modulations of the connectivity from the dACC to the bilateral IFG induced by No-Go trials was identified as the best fitting model in both treatment conditions. DCM further revealed that heroin acutely reduced the inhibition-induced connectivity from the dACC to the right IFG. Dysfunctional ACC connectivity (Liu et al., 2009), as well as abnormal

functional connectivity between the ACC and PFC has also been shown in chronic heroin users during resting state (Ma et al., 2010). These results suggest that impaired inhibitory control in heroin addiction cannot solely be attributed to abnormal ACC activity but may also result from dysfunctional network connectivity between the ACC and PFC regions. Previous theories of cognitive control propose that when erroneous or conflicting behaviour is detected by the ACC, it signals to the lateral PFC responsible for maintaining goal-directed behaviour that greater levels of control are necessary to successfully perform a task (Botvinick et al., 2001). Increased top-down control should reduce conflict by biasing the system away from the incorrect, conflict-causing responses and towards the correct conflict-reducing responses. Therefore, our finding of reduced connectivity from the ACC to the right IFG induced by acute heroin injection suggests a failure of top-down control of the ACC over PFC regions during response inhibition. As a consequence patients under acute heroin exposure were not able to adapt their performance as a result of previously given incorrect responses. One point of contention may be that significant different pattern of brain activation and connectivity were found between the heroin and placebo treatment, while no difference in behavioural performance could be observed. However, differences in brain activity without a change in behavioural performance is a consistent finding in fMRI research (Wilkinson and Halligan, 2004), and can be explained by the fact that fMRI data on small subject numbers are relatively robust (Friston et al., 1999), while behavioural indexes are typically underpowered.

Response inhibition vs. attention allocation

A recent meta-analysis showed that most of the activity typically elicited by No-Go signals, including ACC responses, is actually driven by the engagement of high attentional or working memory resources and not by inhibitory processes *per se* (Criaud and Boulinguez, 2013). In accordance, it has been proposed that the ACC directs attention by modulating activity in diverse cortical regions such as the IFG (Badgaiyan and Posner, 1998; Bush et al., 2000). This corresponds with previous evidence assigning the ACC (Peterson et al., 1999) and its bidirectional connectivity to the right PFC a central role in top-down attentional-control processes (Kondo et al., 2004; Brázdil et al., 2007; Wang et al., 2010). As heroin abuse is associated with deficits in attentional set-shifting (Ornstein et al., 2000) and that opiate-dependent participants actively enrolled in a methadone maintaining programme showed reduced selective attention (Bracken et al., 2012), our results might indicate that the acute heroin effects on dACC activity and on the connectivity from the dACC to the right IFG modulate stimulus-driven attention allocation rather than response inhibition *per se*. This complies with our previous interpretation that heroin administration acutely impairs stimulus-driven attention allocation, as indicated by a reduced IFG activity in response to infrequently presented stimuli, and does not specifically modulate IFG activity during response inhibition (Schmidt et al., 2013c). In brief, we propose that acute heroin administration impairs attention allocation during the Go/No-Go task as expressed by the reduction in dACC activity and functional connectivity from the dACC to the right IFG. Supportive for this interpretation, a recent resting-state fMRI investigation found decreased functional connectivity between the dACC and IFG in heroin-dependent subjects (Wang et al., 2013). They concluded that this dysfunctional connectivity indicates that heroin addicts may have difficulty in attentional allocation or attentional modulation, reflecting a neurophysiological substrate for characteristic pattern of behaviour in heroin addicts.

Underlying pharmacology

It has been shown that long-term opioid-maintained dependents reveal reduced glutamate concentrations in the dACC (Yücel et al., 2007), an effect that is associated with the number of previous withdrawals (Hermann et al., 2012). Furthermore, glutamatergic neurotransmission at the NMDA receptor contributes to the development, expression and maintenance of opioid dependence, suggesting that NMDA receptor antagonists may be a useful adjunct in the treatment of opioid dependence (Noda and Nabeshima, 2004). A previous study in rats showed that acute morphine treatment decreased levels of glutamate in the ACC (Hao et al., 2005). It is therefore conceivable that our heroin effects were partly due to heroin-induced alterations of the NMDA receptor dependent glutamate level in the ACC, also because mu-opioid receptor and NMDA receptor mediated signals are crucially interlinked in opioid dependence (Garzón et al., 2012).

Limitations

We restricted our connectivity analysis on fronto-cingulate connections although a number of outside PFC regions are involved in response inhibition or attentional control. Furthermore, we explicitly focused on the inhibition-induced modulation of connectivity by using bilinear DCM without considering heroin-induced changes on the driving input, endogenous connections or nonlinear modulations, which warrants further investigations. The inhibition-induced modulatory effect was relatively small, although significantly reduced by heroin. The small size of connection parameter might be related to the fast event-related design and the short event durations. Although this study was designed to investigate the acute effect of a daily dose of heroin in patients enrolled in a maintaining programme, comparison with a healthy control group would significantly strengthen the impact of our results.

Conclusions

In conclusion, this is the first fMRI study combining univariate data analysis and effective connectivity modelling to examine the acute heroin effect on response inhibition in heroin-dependent patients. Our findings show that heroin administration acutely reduces dACC activity and related effective connectivity to the right IFG during the Go/No-Go task. Unravelling the role of ACC activity and related brain connectivity may provide valuable insights into pathophysiological mechanisms underlying impaired cognitive control and compulsive drug intake in drug addiction. Further studies are needed to disentangle the acute heroin effects in dependent patients on inhibitory processes and general attentional processes, as well as in comparison with healthy controls.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145714000297

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Conflict of Interest

None.

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